

The role of antifungal treatment in hematology

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Invasive fungal diseases, especially those caused by molds, show many similarities with lymphomas and other hematologic cancers. Indeed, unequivocal proof for the presence of these life-threatening diseases relies on histopathological evidence or on the demonstration of malignant cells or fungi by microscopic examination or culture. In general, if left untreated, these diseases will disseminate and prove fatal. Before adequate treatment is started, a staging workup in search of metastatic lesions needs to be performed, usually involving (but not limited to) whole body computed tomography (CT) scanning, with or without positron emission tomography, and a thorough examination of sanctuary sites. In addition, prognostic scores are constructed at baseline and immunophenotypic profiles, cytogenetic, molecular or serologic markers are identified. The latter may have prognostic value or later serve as surrogate markers for detecting residual disease or for guiding further therapy. First-line therapy typically consists of a single drug or combination of drugs, including the use of monoclonal antibodies or immunomodulatory drugs. Moreover, successful first-line therapy is frequently followed by maintenance therapy for several months, with or without adjunctive radiotherapy or surgery. In case of refractory disease or relapse, salvage treatment is started using drugs with different modes of action. Finally, the crude mortality rate of invasive fungal disease is not that different from the mortality rate of most malignant blood disorders, being around 40%. However, assessing the role of the underlying malignant disease or of invasive fungal disease remains difficult, especially when a postmortem examination is not carried out.

Despite the obvious similarities, clinicians seem to accept different thresholds for initiating diagnostic workups and for starting treatment. Virtually no hemato-oncologist would consider starting antineoplastic chemotherapy, immunotherapy or radiotherapy to prevent the development of malignant disease in a population at risk, or to 'treat' a strong clinical suspicion that the patient may have malignant disease, even if their decision is based on a marker in the absence of histopathological evidence. However, a large majority of these physicians are apparently willing to start expensive broad-spectrum antifungal agents for these exact indications, irrespective of the immediate and long-term consequences, be they in terms of cost, the development of resistance or toxicity. This liberal approach developed in the early 1980s and was fueled by the lack of reliable non-invasive diagnostic tools, a reluctance to look for tissue-based evidence in cytopenic patients, and the impression that early treatment would result in better outcome.

Over the last few decades, four basic strategies have been developed and investigated in clinical studies to deal with

invasive fungal disease, particularly in neutropenic patients. As far as invasive mold disease is concerned, it is possible to delineate various patterns that are encountered in the neutropenic population (Table 1) based on radiological signs and clinical symptoms that might be consistent with invasive fungal disease, and on mycology results, with a view to assessing whether or not they are consistent with infection, disease or both. Each pattern is evaluated for its compatibility with infection and disease, and whether or not it meets the current EORTC/MSG definitions.¹ Management options are also assigned to each pattern. The diagnosis is predicated from a CT scan, and also by testing for evidence of infection directly by culture, and indirectly by testing for galactomannan, though PCR and beta-d-glucan might be included as well. Categories from A through to E each progress along an axis of certainty of diagnosis of invasive fungal disease. Whilst category A represents no invasive fungal disease at all, category E represents proven invasive fungal disease according to current EORTC/MSG definitions. Categories B, C and D represent the spectrum in between these two extremes. Category A is made up of patients who might be considered suitable candidates for prophylaxis,² and category B includes those patients who typically receive empirical antifungal therapy because of persistent unexplained fever despite treatment with broad-spectrum antibacterial therapy.³ Although there is no clinical or microbiological evidence of an invasive fungal disease, this cannot be excluded. Category C merits a more diagnostic-oriented approach (often erroneously called 'pre-emptive' therapy), while categories D and E would receive directed treatment. In clinical practice, these strategies are not mutually exclusive, but rather represent a continuous spectrum of antifungal approaches which may show some considerable overlap. More recently, the focus has clearly shifted towards early antifungal intervention, especially in view of the dismal outcome of treating more advanced invasive fungal disease.

The aim of antifungal prophylaxis (the use of antifungals for patients considered to be at high-risk, usually at therapeutic doses, except for aerosolized formulations) is to prevent invasive fungal infection occurring, or to prevent infections evolving into invasive fungal disease and to improve short-term survival. This has best been demonstrated for fluconazole in stem cell transplant recipients⁴ and for posaconazole in acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS) patients receiving remission-induction chemotherapy.⁵ However, the apparent beneficial impact of posaconazole prophylaxis on overall survival has never been supported by a multivariable regression analysis that takes into account the impact of the status and extent of the underlying disease that are probably the strongest predictors of

outcome. Moreover, the reduced incidence of invasive *Aspergillus* disease in patients receiving a mold-active antifungal may be partly explained by the lower performance of the galactomannan ELISA assay in this setting. For future studies, fungal colonization, incidence of invasive fungal disease, and disease-free survival are probably more appropriate end points than mortality, provided that the study is performed in a blinded-fashion (preferably placebo-controlled) and incorporates a predefined mandatory diagnostic algorithm in both study arms. Infection-related end points are better indicators of prophylactic effectiveness than mortality, as the latter is strongly influenced by the status and severity of the underlying disease. Nevertheless, an Australian observational study by Ananda-Rajah and colleagues comparing fluconazole/itraconazole versus voriconazole/posaconazole prophylaxis in AML/MDS patients supports the main findings of the clinical trial, namely a lower incidence of breakthrough invasive fungal disease (including possible diseases), and less empirical antifungal therapy.⁶ In addition, posaconazole prophylaxis also resulted in a lower demand for CT scans, and when a chest CT scan was taken, fewer lesions were seen. However, unselected use of broad-spectrum antifungal prophylaxis also raises concerns about expenditure, overtreatment, toxicity and emergent drug-resistance. Furthermore, better knowledge of institutional fungal epidemiology and further refinements to the identification of patients most likely to benefit from antifungal prophylaxis (i.e. what constitutes high-risk in terms of likelihood of developing invasive fungal disease and what is an acceptable number needed to treat), would represent a major advance in our efforts to reduce the drawbacks associated with routine prophylaxis. As a result, antifungal prophylaxis practice varies

considerably among different centers and remains the subject of lively debate.⁷

For a long time, profound and prolonged neutropenia accompanied by persistent or relapsing fever has been regarded as a sufficient trigger for starting broad-spectrum antifungals; a strategy referred to as empirical antifungal therapy. This practice has never been supported by robust scientific evidence and has important drawbacks, including drug-related toxicity and increased cost. In spite of this, the empirical use of antifungals has become the standard of care in many hematology centers. It was also endorsed by consensus guidelines and is relied on by centers that have limited or no access to radiological and mycological diagnostic tools. A prospective study from Spain by Aguilar-Guisado and colleagues challenges this undifferentiated approach.⁸ The study established the feasibility of a more tailored diagnostic and therapeutic approach based on clinical criteria other than fever. The strategy had an excellent negative predictive value (correct identification of patients not needing antifungal therapy) for febrile neutropenic patients, resulting in a marked reduction in antifungal consumption without an increase in the overall mortality or fungal-related mortality. These results are in line with those of other studies in this setting using radiological features or microbiological test results or both to trigger the initiation of antifungal therapy.^{9,10} However, despite the significant global reduction in antifungal usage compared to the classic empirical approach, these new strategies still have low specificity. Consequently, a large proportion of patients will continue to receive antifungal therapy unnecessarily.

Given that the cupboard of antifungals is bare and there are few in the pipeline, future efforts should focus on the development and incorporation of tests to increase the

Table 1. Patterns of invasive fungal disease in practice, based on 2008 EORTC-MSG criteria.

	A		B		C				D		E
	-	-	I	II	III	IV	-	-	-	-	
Radiological signs and clinical symptoms	No	Persistent febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)			Radiological signs on CT (dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity)		Not considered necessary		
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Positive biomarker or microscopy or culture	Positive tissue or specimen from a sterile site		
Clinical evidence of IFD	No	No	No	No	No	Yes	Yes	Yes	Yes		
Mycological evidence of IFI	No	No	Yes	No	Yes	No	Yes	Yes	Yes		
Final diagnosis	Unclassified					Possible IMD	Probable IMD	Proven IMD			
Management	Prophylaxis	Empirical therapy	Diagnostic-driven (pre-emptive) therapy				Targeted therapy				

specificity of the diagnostic approach. The availability of a clinically validated test for detecting fungal DNA would be very welcome. The adoption of explicit care pathways would also help establish a standard that achieves a more favorable balance between effectiveness and cost.¹¹ It is also true that there will be no paradigm shift without evidence from properly conducted prospective strategy trials. Non-randomized studies have identified some of the logistical hurdles. For instance, a diagnostic-oriented approach requires the availability of diagnostic tests with a rapid turnaround and the full cooperation and compliance of all parties involved (be they clinicians, microbiologists, radiologists, nurses, or pharmacists) as well as a strict adherence to minimum standards of diagnosis as envisaged in integrated care pathways.¹² Validation of these more targeted approaches is clearly required, but will only be possible if health care providers combine their efforts with those of researchers to establish a consortium to support such studies. This is essential if we are to evaluate a standardized diagnostic approach that has already gained wide acceptance but has not yet been formally examined. Fortunately, such endeavors are currently ongoing in Europe; for instance, the multicenter strategic study of empirical *versus* pre-emptive antifungal therapy of patients with hematologic malignancies of the EORTC Infectious Diseases Group. However, even if successful, this study will likely only meet the needs of European institutions. There is also a pressing need to explore antifungal strategies in other clinical settings both in Europe and in other parts of the world, as invasive fungal diseases are likely to remain an unwelcome companion when treating malignancies, managing immunodeficiencies, and delivering transplants of stem cells and organs.

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